Improved Survival in Women with *BRCA*-Associated Ovarian Carcinoma

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BACKGROUND. The objective of this study was to determine the clinical characteristics, treatment response, and frequency of *p53* overexpression in Ashkenazi Jewish women with hereditary ovarian carcinoma.

METHODS. Seventy-one Jewish women with epithelial ovarian carcinoma (EOC) were tested for the three *BRCA* founder mutations using single-strand conformation polymorphism analysis, heteroduplex analysis, and protein truncation testing. Clinical and histopathologic data were reviewed retrospectively. In vitro chemoresistance was analyzed in 32 patients. Mutations of *p53* were studied using immunohistochemical detection of *p53* overexpression.

RESULTS. Thirty-four of 71 Jewish patients with EOC (48%) had germline *BRCA* mutations (*BRCA* heterozygotes), including 22 *BRCA1* mutations and 12 *BRCA2* mutations. *BRCA* heterozygotes were younger compared with Jewish patients who had EOC without mutations (sporadic carcinoma; 50 years vs. 59 years, respectively; $P = 0.01$). *BRCA1* heterozygotes were younger compared with *BRCA2* heterozygotes (48 years vs. 57 years, respectively; $P = 0.01$). Histopathologic tumor features were similar; however, tumors with low malignant potential were seen only in women with sporadic carcinoma. Both groups had equivalent rates of surgical cytoreduction and similar median follow-up (72 months). *BRCA* heterozygotes had higher response rates to primary therapy compared with patients who had sporadic disease ($P = 0.01$). In vitro chemoresistance predicted tumor response to platinum chemotherapy correctly in *BRCA* heterozygotes ($P = 0.0096$). *BRCA* heterozygotes with advance-stage disease had improved survival compared with patients who had advanced stage sporadic carcinoma (91 months vs. 54 months, respectively; $P = 0.046$) and had a longer disease free interval (49 months vs. 19 months, respectively; $P = 0.16$). *p53* overexpression was common in *BRCA* heterozygotes (80%).

CONCLUSIONS. *BRCA1* heterozygotes developed EOC at a younger age compared with BRCA2 heterozygotes and women who had sporadic ovarian carcinoma. *BRCA* heterozygotes had a better response to platinum chemotherapy compared with women who had sporadic disease, which may have contributed to their improved prognosis. ***Cancer* 2003;97:2187–95.** © *2003 American Cancer Society.*
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KEYWORDS: hereditary ovarian carcinoma, chemosensitivity, *BRCA*1, *BRCA*2, *p53*.

Approximately 10% of invasive ovarian carcinomas are due to genetic predisposition and are associated with an inherited mutation in either the *BRCA1* gene or the *BRCA2* gene.[1] In some populations, the prevalence is greater; in particular, among Ashkenazi Jewish women with ovarian carcinoma, the hereditary proportion approaches 50%.[2–4] Approximately 2% of Ashkenazi Jewish women carry one of the three founder mutations in *BRCA1* or *BRCA2*.[5–7] Female carriers of *BRCA1* mutations have a 16–44% lifetime risk of develop-

ing ovarian carcinoma, and *BRCA2* mutation carriers have a 16–27% risk.[8–11]

Evidence suggests that the *BRCA* genes act as tumor suppressor genes and regulate cellular proliferation and DNA repair by maintaining chromosomal integrity.[12–14] In vitro and animal model data have demonstrated that diminished *BRCA* gene product is associated with chromosomal instability and increased proliferative rate of epithelial breast carcinoma cells.[15,16] This observation has led investigators to hypothesize that *BRCA* mutations may impact on tumor biology and clinical behavior.

Several studies have compared the molecular and clinical characteristics of *BRCA*-associated ovarian tumors with the same characteristics in patients with sporadic ovarian tumors. Hereditary *BRCA*-associated and sporadic ovarian carcinomas appear to have similar histopathologic characteristics; however, a greater proportion of hereditary ovarian carcinomas carry *p53* mutations.[17–19] Molecular analyses of *BRCA*-associated tumors have suggested potential distinctions between the carcinogenic pathways of hereditary *BRCA*-associated and sporadic breast and ovarian carcinomas.[20,21]

Several studies have demonstrated better survival for patients who had hereditary *BRCA*-associated ovarian carcinoma compared with patients who had sporadic ovarian carcinoma.[22–24] Two of the largest series used genetic testing for the three common *BRCA1* and *BRCA2* founder mutations in predominantly Ashkenazi Jewish populations with ovarian carcinoma to study clinical outcome prospectively in women with BRCA mutations (*BRCA* heterozygotes).[22,23] Smaller, retrospective studies did not find a survival benefit in *BRCA* mutation carriers, although those studies used variable criteria to identify cases and controls.[25–27]

The basis for this survival advantage is unknown. It may relate to the younger average age at diagnosis or the different profile of molecular alterations among patients with hereditary carcinoma. Alternatively, it is possible that patients with *BRCA*-associated carcinoma have a better response to chemotherapy treatment. This chemosensitivity may be the result of an impaired ability of *BRCA*-deficient cells to repair DNA that is damaged by cytotoxic chemotherapy.[13,28,29] Relatively little data are available on the survival of women with *BRCA2*-associated ovarian tumors.

The objective of this study was to compare the pathologic characteristics, treatment response (including in vitro chemosensitivity assays), and survival outcomes of Ashkenazi Jewish women who had hereditary *BRCA*-associated ovarian carcinoma with the same variables in Ashkenazi Jewish women with sporadic ovarian carcinoma who were treated at a single institution. The benefit of limiting our study population to a single ethnic group was to minimize some of the associated epidemiologic variations that may have an impact on patient survival. Our objective was to determine whether any observed differences in survival could be attributed to differences in tumor characteristics (stage, grade, *p53* mutation status) or were due to clinical response to chemotherapy.

MATERIALS AND METHODS

All women who were of Jewish descent and were treated for primary ovarian carcinoma or papillary serous peritoneal carcinoma between 1990 and 1998 were identified through the Tumor Registry of the Cedars-Sinai Medical Center. Jewish ethnicity was recorded in the medical record or was noted by the treating physician. The treating physicians were asked to write letters or to contact patients directly to request the patient's participation in the study. If the patient was alive and their treating physician agreed, then the patient was approached to participate in the study. A member of the study team then interviewed each patient and confirmed that they were Jewish by birth (i.e., that they were not adopted and had not converted). Other eligibility criteria required that patients had a confirmed diagnosis of epithelial ovarian, tubal, or peritoneal carcinoma. After 1998, the protocol was amended, and patients were identified prospectively from the Tumor Registry and were invited to participate in the study immediately after their primary surgery.

A total of 139 Ashkenazi Jewish women were diagnosed with epithelial ovarian carcinoma or papillary serous peritoneal carcinoma from 1990 to 1998. Potential study participants were ascertained between 1996 and 1998 as living patients who underwent primary surgery at Cedars-Sinai Medical Center. Of 139 possible study participants, 51 women were dead according to the Tumor Registry, and it was not possible to locate 7 patients. Of the remaining 81 women, 27 patients did not participate, either because the treating physician or the patient had concerns regarding insurance or because of the stress of the results. Fifty-four patients consented to interviews with a member of the study team and to have a blood sample drawn for genetic testing. Patients who wished to could have additional genetic counseling for other disorders and were offered the option of receiving their *BRCA* genetic test results at no expense.

From 1999 to 2001, all newly diagnosed Ashkenazi Jewish women with epithelial ovarian carcinoma who underwent primary surgery by a member of the Gynecologic Oncology Division at Cedars-Sinai Medical Center were approached to participate in the study. Of

31 potential participants, 3 women died before consent was obtained, and 11 women refused to participate. Seventeen patients who consented to participate in the study have been followed prospectively.

Demographic Data and Surgical Characteristics

Epidemiologic data on patient demographics and surgical characteristics were extracted from hospital records and patient interviews. Patients were asked to complete a questionnaire about their medical history, ethnic background, and the birthplace of their parents and grandparents. Using the completed questionnaire, three-generation pedigrees were obtained at the time of patient interview to include all women with breast or ovarian carcinoma and their age at diagnosis. The diagnosis of ovarian carcinoma in the proband was confirmed by review of all pathologic reports; however, it was not possible to confirm the diagnoses in relatives.

Primary tumor sites (ovary or peritoneal) were confirmed by review of pathology reports. Tumors were classified as primary papillary serous carcinomas when there was minimal or absent involvement of the ovaries according to established histologic criteria.[30] Surgical stage and histologic grade were classified according to the International Federation of Gynecology and Obstetrics and World Health Organization standards and were determined from the review of patient medical records, operative reports, and pathologic reports.

Analysis of patient survival and tumor response was limited to patients with invasive, advanced-stage (Stage III–IV) disease. Tumor response to primary chemotherapy was defined by three criteria in patients with advanced-stage disease: negative second-look surgery, regression of measurable disease, or clinically free of disease for 5 years after diagnosis. In patients who underwent suboptimal surgical cytoreduction ($>$ 1.0 cm residual disease), clinical tumor regression was defined as normalization of an elevated CA 125 value ($<$ 35 U/mL on two consecutive tests), or by a decrease $>$ 50% in the size of measurable disease on physical examination or radiologic imaging. Patients who underwent optimal surgical cytoreduction ($\leq$ 1 cm residual disease) and did not undergo second-look surgery were not evaluable for tumor response unless they were clinically free of disease for 5 years. Tumor recurrence was defined as a doubling of CA 125 levels $>$ 100 U/mL on two consecutive tests, the appearance of a measurable lesion on examination or radiologic imaging, or histologic evidence of recurrent disease. Disease free intervals were calculated between the date of diagnosis and date of recurrence. Information on patient survival was extracted from patient charts, patient interviews, or from treating physicians. Patients with a past history of malignant disease were included in survival analyses.

Mutation Analysis

High-molecular-weight DNA was isolated from whole blood using standard techniques. Exons 2 and 20 of the *BRCA1* gene and exon 11 of *BRCA2* were amplified by polymerase chain reaction. Exon 20 of *BRCA1* was evaluated for the 5382insC mutation by single-strand conformational polymorphism analysis, and exon 2 of *BRCA1* was evaluated for the 185delAG mutation by heteroduplex analysis. Mutations in exon 11 of *BRCA1* and exons 10 and 11 of *BRCA2* were screened by protein truncation testing. Truncating mutations in these exons represent $>$ 70% of the mutations found to date in families with deleterious mutations. A protein truncation test of exon 11 also was used to identify the abnormal band corresponding to the *BRCA2* 6174delT mutation. All identified mutations were confirmed by sequence analysis.

P53 Mutation Analysis

Paraffin embedded tumor specimens were available for 54 of 71 patients. These tumors specimens were screened for *p53* overexpression using immunohistochemistry. Slides were prepared and stained according to standard protocol.[31] Two independent observers (I.C. and R.L.B.) scored *p53* antigen expression using both intensity and distribution of nuclear staining. Samples were considered positive if $>$ 10% of nuclei within cells were stained.

In Vitro Chemoresistance

In vitro chemoresistance testing was performed on patient's tumors at the discretion of the attending physician. The rationale for chemoresistance assay testing was potentially to assist in the choice of chemotherapy for first-line or second-line treatment. Tumor cells were exposed to a panel of chemotherapeutic agents that have shown activity in ovarian carcinoma, including paclitaxel, cisplatin, and/or carboplatin.[32,33] Tumor cells that continue to proliferate after exposure to supraphysiologic doses of drugs compared with untreated controls have extreme drug resistance to the tested drug. Tumor cells that exhibit some degree of growth inhibition after drug exposure have low or intermediate drug resistance.[34]

Statistical Analysis

Overall survival and disease free survival were estimated using the Kaplan–Meier method, and survival curves were compared using the log-rank test. Medians for time independent outcomes, such as age, were

TABLE 1
Characteristics of Patients with Ovarian Carcinoma

Characteristic	With *BRCA* mutation (heterozygotes)	Sporadic disease	*P*
No. of patients	34	37	—
Median age at diagnosis (yrs)	50	59	0.01
Histology			
Low malignant potential	0	6	0.042
Serous invasive	31	29	ns
Other invasive	3	2	—
Nuclear grade (invasive)			
1	0	3	—
2	2	4	—
3	32	24	ns
Stage (invasive tumors)			
I–II	5	6	—
III–IV	29	25	ns
Primary peritoneal carcinoma	8 (24%)	5 (14%)	ns
CA125 level[a] (U/mL)			
Median preoperative	438	351	ns
Range	14–6450	8–2900	—
Optimal cytoreduction (invasive, Stage III–IV)	26/29 (86%)	24/25 (96%)	ns
Primary chemotherapy	34	30	ns
Median follow-up (mos)	142	72	ns

ns: not significant; LMP: low malignant potential.
[a] Excluding LMP.

TABLE 2
Characteristics of Patients with Ovarian Carcinoma with *BRCA* Mutations (*BRCA* heterozygotes)

Characteristic	*BRCA1* mutation	*BRCA2* mutation	*P*
No. of patients	22	12	—
Age at diagnosis (yrs)			
Median	48	57	0.01
Range	37–81	45–72	—
CA125 level (U/mL)			
Median preoperative	445	423	ns
Range	14–6450	45–1500	—
Stage			
I–II	4	1	—
III–IV	18	11	ns
Median follow-up (mos)	142	75	ns
Optimal cytoreduction:			
Stage III–IV (%)	15/18 (83)	11/11 (100)	ns
Disease free interval:			
Stage III–IV (mos)	40	57	0.2

ns: not significant.

compared using Wilcoxon nonparametric methods. Proportions and categorical variables were compared using Fisher exact methods (exact chi-square test). Differences associated with $P < 0.05$ were considered statistically significant.

RESULTS

Seventy-one Ashkenazi Jewish women with either epithelial ovarian carcinoma ($n = 58$ patients) or with peritoneal serous papillary carcinoma ($n = 13$) were identified at Cedars-Sinai Medical Center. Thirty-four of 71 patients (48%) who were screened had 1 of the 3 Ashkenazi Jewish founder mutations (*BRCA* heterozygotes). Ashkenazi Jewish patients who were without germline mutations served as the comparison (sporadic) group (Table 1). Twenty-six of 58 patients (45%) with epithelial ovarian carcinoma had germline *BRCA* mutations. Eight of 13 patients (61%) with peritoneal carcinoma had germline *BRCA* mutations. Peritoneal carcinomas were more common among *BRCA* heterozygotes than among patients in the sporadic group, (24% vs. 14%, respectively); however, the difference was not statistically significant. The median age at the time of diagnosis in women who had *BRCA* mutations was significantly younger compared with patients without mutations (50 years vs. 59 years, respectively; $P = 0.01$). *BRCA1* mutation carriers were diagnosed 9 years earlier, on average, than *BRCA2* mutation carriers (48 years vs. 57 years, respectively; $P = 0.01$) (Table 2). Among *BRCA* mutation carriers, 36% of women who carried *BRCA1* mutations were diagnosed before age 45 years, whereas no women who carried *BRCA2* mutations were diagnosed at age < 45 years.

A family history of breast and ovarian carcinoma was defined as a first-degree relative with breast or ovarian carcinoma diagnosed at any age. Sixteen of 34 patients (47%) with *BRCA*-associated ovarian carcinomas had a family history of breast or ovarian carcinoma compared with 3 of 37 patients (8%) with sporadic ovarian carcinoma ($P = 0.001$). Six of 34 (18%) *BRCA* heterozygotes had a personal history of breast carcinoma, which was bilateral in 1 patient. Three of 37 patients (8%) with sporadic ovarian carcinoma had a personal history of breast carcinoma.

Three incident breast carcinomas were observed during follow-up in two *BRCA*-mutation carriers with ovarian carcinoma and in one patient in the sporadic ovarian carcinoma group. The actuarial survival rate for patients who developed breast carcinoma subsequent to a diagnosis of ovarian carcinoma did not demonstrate a statistically significant difference between *BRCA* mutation carriers and noncarriers ($P = 0.6$).

The histologic and clinical features of the *BRCA* heterozygotes and sporadic carcinoma patients were similar, with the exception of the frequency of tumors with low malignant potential (Table 1). Tumors with low malignant potential were seen only among nonmutation carriers ($P = 0.042$). The majority of patients had advanced-stage, high-grade, serous carcinomas.

Fifty of 54 patients with advanced-stage disease (Stage III–IV) underwent cytoreductive surgery by a gynecologic oncologist. Optimal cytoreduction was achieved in 26 of 29 patients (90%) in the group of *BRCA* heterozygotes with ovarian carcinoma and in 24 of 25 patients (96%) with sporadic ovarian carcinoma.

All 54 patients with invasive, advanced-stage disease (Stage III–IV) were treated with combination platinum-containing chemotherapy regimens. Fourteen patients with ovarian/peritoneal carcinoma (7 *BRCA* heterozygotes and 7 patients in the sporadic group) were diagnosed before 1994 and were treated with cytoxan and carboplatin. The remaining 40 patients, who were diagnosed after 1994, were treated with paclitaxel and carboplatin. Equivalent numbers of patients in each cohort received second-line and third-line chemotherapy.

Preoperative CA 125 levels were available for 28 of 34 patients (82%) with *BRCA*-associated, invasive ovarian/peritoneal carcinoma and for 23 of 31 patients (74%) with sporadic, invasive ovarian/peritoneal carcinoma. There was no statistical difference in the median CA 125 values of the two groups (438 U/mL vs. 351 U/mL, respectively; $P = 0.9$) (Table 1). The median CA 125 values for *BRCA1* and *BRCA2* mutation carriers were similar (445 U/mL vs. 423 U/mL, respectively), although the significance if this finding is unclear, because patient numbers were small (Table 2).

Surgical outcome in relation to CA 125 levels was analyzed in both groups of patients using a threshold preoperative CA 125 value of < 500 U/mL or > 500 U/mL. Preoperative CA 125 levels > 500 U/mL were observed in 36% of all patients with *BRCA*-associated ovarian/peritoneal carcinoma and in 52% of patients with sporadic ovarian/peritoneal carcinoma. CA 125 levels > 500 U/mL did not predict optimal surgical cytoreduction, defined as $\leq$ 1cm residual disease, in patients with *BRCA*-associated or sporadic, advanced-stage disease. All patients with CA 125 levels > 500 U/mL achieved optimal cytoreduction: 7 *BRCA* mutation carriers and 11 patients in the sporadic group.

The median survival of patients with invasive, advanced-stage, *BRCA*-associated ovarian/peritoneal carcinomas was 91 months, compared with 54 months among patients in the group with sporadic disease ($P = 0.046$) (Fig. 1). The 2-year and 5-year survival rates were significantly better among patients with *BRCA*-associated than among patients in the sporadic control group (Table 3). The median disease free interval among patients with invasive, advanced-stage (Stage III–IV) *BRCA*-associated carcinoma was 49 months compared with 19 months among patients with sporadic carcinoma, which approached statistical significance ($P = 0.16$) (Fig. 2).

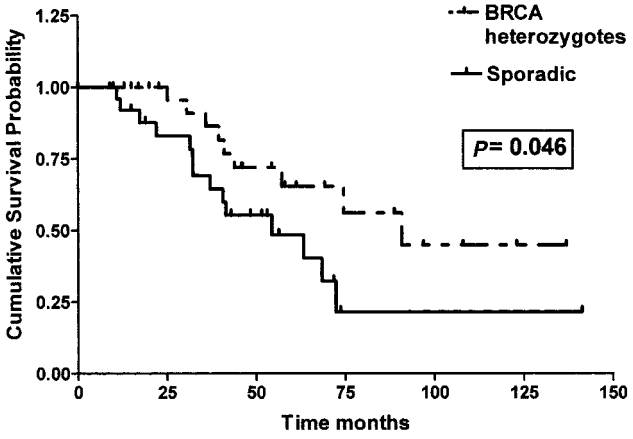

FIGURE 1. Overall survival of women who had advanced-stage (Stage III–IV) ovarian carcinoma with germline *BRCA* mutations (BRCA heterozygotes) compared with women who had sporadic ovarian carcinoma (Sporadic).

TABLE 3
Comparison of Treatment Outcome between Jewish Patients with Advanced Stage (III–IV) Ovarian Carcinoma With and Without *BRCA* Mutations

Characteristic	*BRCA* mutation (heterozygotes) ($n = 29$)	Sporadic disease ($n = 25$)	*P*
No. of patients with recurrence	21 (72%)	21 (84%)	ns
Survival			
Median DFI (mos)	49	19	0.16
Two-year survival (%)	100	83	—
Five-year survival (%)	65	48	—
Response			
No. of responses[a]	21	9	—
No. of nonresponses	3	10	0.01
Second-look surgery			
Negative	18	7	—
Positive	3	10	0.01

ns: not significant; DFI: disease free interval.

[a] Tumor responses included either negative second-look surgery, regression of measurable disease, or no evidence of disease > 5 years.

BRCA mutation carriers had higher rates of tumor response compared with patients in the sporadic control group (Table 3). *BRCA* heterozygotes were more likely to have a negative second-look surgery compared with patients in the sporadic group: 18 of 21 patients (86%) versus 7 of 17 patients, respectively (41%; $P = 0.01$). Tumor response was observed in three additional *BRCA* heterozygotes and in two patients with sporadic ovarian carcinoma based on clinical regression of measurable disease or on maintaining clinical disease free status for 5 years. The total response rate, including negative second looks and clinical responses, among *BRCA* heterozygotes was significantly better compared with the tumor response

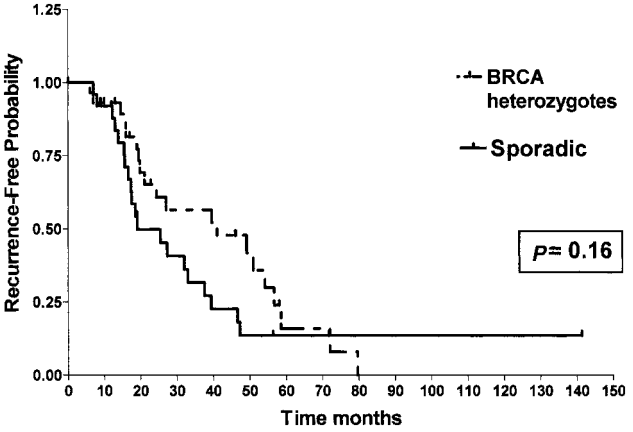

FIGURE 2. Disease free interval for women who had advanced-stage (Stage III–IV) ovarian carcinoma with germline *BRCA* mutations (*BRCA* heterozygotes; BRCA MUT) compared with women who had sporadic ovarian carcinoma (Sporadic).

among patients in the sporadic control group ($P = 0.01$).

Analysis of clinical outcome by *BRCA1* or *BRCA2* mutation revealed comparable findings (Table 2). The histologic features of the ovarian/peritoneal carcinomas among *BRCA1* and *BRCA2* mutation carriers were similar, and each had equivalent rates of optimal cytoreduction. A comparison of disease free interval and rates of recurrence was limited by the small number of patients with advanced-stage, *BRCA1* and *BRCA2* mutation carriers: 18 patients and 11 patients, respectively. Nevertheless, *BRCA2* mutation carriers had a marginally longer disease free interval compared with *BRCA1* mutation carriers: 57 months versus 40 months, respectively ($P = 0.2$).

In vitro chemoresistance assay results were available for 18 patients with *BRCA*-associated ovarian carcinoma and 14 patients with sporadic ovarian carcinoma (Table 4). Equivalent proportions of patients with ovarian carcinoma in the group of *BRCA* heterozygotes and in the sporadic group had predicted high drug resistance to platinum: 5 of 18 patients (28%) versus 3 of 14 patients (21%), respectively. Low/intermediate predicted in vitro resistance to platinum in patients with ovarian carcinoma was correlated with tumor response in the group of *BRCA* heterozygotes but not in the group with sporadic disease (odds ratio [OR], 25; 95% confidence interval [95%CI], 1.2–536; $P = 0.01$). Similarly, low/intermediate predicted in vitro resistance to paclitaxel in patients with ovarian carcinoma was correlated with tumor response in the group of *BRCA* heterozygotes but not in the group with sporadic disease (OR, 19; 95%CI, 1.0–415; $P = 0.026$). In vitro chemoresistance assays that predicted high resistance to platinum or paclitaxel did not identify the patients with disease persistence or progression in either cohort, although the validity of this finding is uncertain, because patient numbers were very small in this group.

TABLE 4
Low/Intermediate in Vitro Response Assays Correlated with Tumor Response in Patients with Ovarian Carcinoma who had *BRCA* Mutation or Sporadic Disease

	Low/intermediate predicted in vitro resistance		
Response	***BRCA* mutation**	**Sporadic disease**	***P***
Platinum drugs			
In vivo tumor response			
Yes	12	5	—
No	0	5	0.01
Paclitaxel			
In vivo tumor response			
Yes	11	5	—
No	0	4	0.026

Overexpression of *p53* was evident in 23 of 29 patients (79%) who had *BRCA*-associated ovarian carcinoma, compared with 15 of 25 patients (60%) who had sporadic ovarian carcinoma ($P = 0.15$). Among the patients with advanced-stage disease, 20 of 25 patients (80%) with *BRCA* associated carcinomas had *p53* overexpression, compared with 13 of 20 patients (65%) with sporadic disease. Clinical outcome was analyzed by *p53* mutation status to determine whether *p53* mutation affected survival. Patients with *p53* overexpression had a slightly improved survival, but the difference did not achieve statistical significance ($P = 0.2$). Limiting the population to patients with advanced-stage, *BRCA*-associated ovarian carcinoma, *p53* mutation status was not correlated with patient survival.

DISCUSSION

Patients who had advanced-stage *BRCA*-associated ovarian carcinoma had significantly improved survival compared with the control group of patients who had sporadic ovarian carcinoma. The survival advantage of patients with *BRCA*-associated ovarian carcinoma in our study could not be attributed to less aggressive disease, as predicted by established clinical prognostic factors in patients with ovarian carcinoma. The only notable histologic difference between *BRCA*-associated ovarian carcinoma and sporadic ovarian carcinoma was the absence of low malignant potential tumors in *BRCA* mutation carriers. Based on the low frequency of tumors with low malignant potential

among *BRCA* mutation carriers in other large series, it appears that tumors of low malignant potential are not part of the *BRCA*-associated tumor phenotype.[23,35]

Preoperative CA 125 levels were not a useful discriminator of optimal surgical cytoreduction in patients with either *BRCA*-associated carcinoma or sporadic carcinoma, which may relate to the high rates of optimal surgical cytoreduction in our study.[36] Very few studies of clinical outcome in patients with *BRCA*-associated ovarian carcinoma have provided adequate detail regarding tumor stage or rates of surgical cytoreduction.[24–27,37] Given the critical prognostic value of these variables in patients with ovarian carcinoma, studies that do not adjust for tumor stage or residual disease in their analysis of patient survival must be interpreted with caution.[38] The studies that have employed contemporary therapy with adequate follow-up have found improved survival for patients with hereditary *BRCA*-associated ovarian carcinomas.[22–24]

In contrast to other studies, we found that patients with *BRCA*-associated carcinomas had better tumor response compared with patients in the sporadic control group using stringent pathologic and clinical criteria. We hypothesize that the improved survival of patients with *BRCA*-associated carcinomas results from enhanced tumor response to combination platinum-based chemotherapy rather than less aggressive tumor characteristics. In vitro chemoresistance was more useful in predicting tumor response to platinum chemotherapy among patients with *BRCA*-associated tumors than among patients with sporadic tumors. Although the utility of in vitro chemoresistance assays remains controversial in patients with ovarian carcinoma, further study may be warranted in patients with *BRCA*-associated carcinomas.[32,33]

The molecular mechanisms that explain the improved prognosis for patients with hereditary, *BRCA*-associated ovarian carcinoma are unknown but may be related to the function of *BRCA* genes. Recent data suggest that *BRCA* genes play an important role in cell-cycle checkpoint activation and in the repair of damaged DNA.[13,14,39] Preclinical data have demonstrated that *BRCA1* impacts chemosensitivity in breast and ovarian carcinoma cell lines. Husain et al. restored cisplatin chemosensitivity in cisplatin-resistant ovarian carcinoma cell lines with antisense inhibition of *BRCA1*, which reduced *BRCA* protein expression.[28] Recent clinical data suggest that enhanced chemosensitivity in patients with *BRCA*-associated ovarian carcinoma may result from a higher tumor growth fraction compared with tumor samples from patients with sporadic ovarian carcinoma.[40]

Coexisting mutations in other tumor suppressor genes may contribute to ovarian carcinogenesis and patient outcome in *BRCA* mutation carriers. Given the critical role of *p53* in cell cycle regulation, it has been postulated that *BRCA1* and *p53* may act in concert to control aberrant cellular growth.[41–44] Data suggests that *p53* mutation may facilitate malignant transformation of the *BRCA* mutant cell.[45,46] Clinical studies have confirmed a high frequency of *p53* mutations in hereditary BRCA-linked breast carcinoma and ovarian carcinoma, but there are limited data indicating whether *p53* mutation status has an impact on the clinical outcome of patients with hereditary, *BRCA*-linked ovarian carcinoma.[17–19,47,48] We detected a high frequency of *p53* overexpression in patients with *BRCA*-associated ovarian carcinoma using immunohistochemistry. The most frequent *p53* mutations, missense and in-frame deletions, are detected readily with immunostaining analysis.[17,18,49] The observed differences in survival between carriers of *BRCA* mutations and women with sporadic disease could not be attributed to *p53* mutation status. Although the correlation of *p53* mutation status and clinical outcome in patients with advanced-stage ovarian carcinoma remains unclear, *p53* mutation is a known adverse prognostic factor in patients with breast carcinoma.[49,50] Small clinical studies found decreased response rates to cisplatin-based therapy among patients with ovarian carcinoma patients who had *p53* mutations.[51,52] Based on these observations, we currently are investigating the effects of *BRCA* and *p53* mutations on chemosensitivity in *BRCA* competent and mutant ovarian carcinoma cell lines and primary cultures derived from this group of patients using several different cytotoxic drugs.

In agreement with other reports, our data demonstrate that Jewish *BRCA* mutation carriers develop ovarian carcinoma at a younger age compared with Jewish patients who have sporadic ovarian carcinoma. After stratifying the 34 patients with germline *BRCA* mutations by mutant gene, further analysis revealed that this difference is explained by the significantly younger age at diagnosis of the *BRCA1* mutation carriers compared to *BRCA2* mutation carriers. Previous studies suggested that *BRCA1* mutation carriers develop ovarian carcinoma 6–9 years earlier than *BRCA2* mutation carriers.[4,22,27] This finding has significant implications for counseling *BRCA* mutation carriers regarding the timing of preventative interventions. The timing of prophylactic oophorectomy may vary based on *BRCA* mutation genotype to optimize patient fertility and hormonal status.

In light of the high probability of *BRCA* mutations in Jewish patients with ovarian carcinoma, we currently discuss genetic testing with all newly diagnosed, Jewish patients with ovarian/peritoneal or fallopian

tube carcinoma. A family history of breast or ovarian carcinoma was much more common among patients with hereditary, *BRCA*-associated ovarian carcinoma than among patients with sporadic disease; however, the majority of patients with *BRCA*-associated ovarian carcinoma did not have any family history of breast carcinoma or ovarian carcinoma. Certainly there are potential benefits to family members in identifying individuals with high risk and employing strategies to prevent disease (chemoprevention, screening programs, and prophylactic surgery).

These patients must be counseled regarding their ongoing risk of developing a subsequent breast carcinoma as survival improves for women with ovarian carcinoma. To date, three of nine patients (33%) with both breast carcinoma and ovarian carcinoma in our series have been diagnosed with breast carcinoma after they were diagnosed with ovarian carcinoma. Given the heightened risk of breast carcinoma associated with *BRCA* mutations, *BRCA* heterozygotes with ovarian carcinoma should have increased breast carcinoma surveillance and should consider chemoprevention and/or prophylactic mastectomy.[11,53,54]

Further study with larger patient populations will be necessary to confirm improved survival in patients with *BRCA*-associated ovarian carcinoma and to better elucidate the biologic basis of this survival advantage. Like several studies, the initial retrospective design of our study suffered from selection bias by including only living patients with ovarian carcinoma.[24–27] We recognize the limitation of studying survival as an endpoint in a group of ovarian carcinoma survivors. Therefore, we have amended the study to prospectively follow all newly diagnosed Jewish patients with ovarian, peritoneal, or tubal carcinoma.[55] If *BRCA* mutation confers a better prognosis for patients with ovarian carcinoma or predicts improved response to certain chemotherapeutic agents, then this information may be useful for the clinician in planning the patient's treatment and in the selection of patients for clinical trials.

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